Cardiovascular Oncology
From the perspective of an oncologist

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Medical Oncologist
The Ottawa Hospital Cancer Center
Professor of Medicine, University of Ottawa
February 22nd, 2017
17th Annual Benjamin Schuster, MD Colloquium
Objectives

• To discuss the impact of cancer treatments on the heart
• To discuss strategies to optimize cardiac health in cancer patients
• To discuss the benefits of a multidisciplinary approach in management of these patients
Predicted global cancer cases

Source: WHO GloboCan
**The big C**

Drugs in development*, 2010

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>1,000</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Pain and inflammation</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Diabetes and metabolism</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Blood disorders</td>
<td></td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
</tr>
</tbody>
</table>

*Top ten therapeutic areas for the world’s big pharmaceutical firms, includes drugs in Phase I, II, III or awaiting FDA approval.

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**Estimated Number of Cancer Survivors in the US**

![Graph showing the estimated number of cancer survivors in the US from 1970 to 2020.](image)

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[cardiaconcology.ca](cardiaconcology.ca)
WHOA! EASE UP ON THE CHEMO, NURSE. THAT'S HOW MUCH WE USE TO EUTHANIZE HORSES.

FACT:
CHEMOTHERAPY CHEMICALS CAUSE PERMANENT DAMAGE TO THE HEART, LIVER AND KIDNEYS.

WWW.NEWSTARGET.COM
“The cured cancer patient of today does not want to become the heart failure patient of tomorrow.”

Cardiovascular events in cancer survivors

Incidence of cardiac events in pediatric cancer survivors

Helena J. van der Pal et al. JCO 2012

Cardiovascular Disease: Important cause of mortality in early breast cancer

Cardiotoxicity of Chemotherapy Drugs

Table 1: Systemic cancer drugs with important cardiovascular side effects; selected indications

<table>
<thead>
<tr>
<th>Class/drugs</th>
<th>Selected indications</th>
<th>Important CV side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytostatic chemotherapeutics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracyclines/analogues</td>
<td>Lymphoma</td>
<td>Cardiac dysfunction/heart failure</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Leukaemia</td>
<td></td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Breast cancer</td>
<td></td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Ovarian cancer</td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Sarcoma</td>
<td></td>
</tr>
<tr>
<td>Pyrimidine analogues</td>
<td>Leukaemia</td>
<td></td>
</tr>
<tr>
<td>Fluorouracil (5-FU)</td>
<td>Multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylating agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimicrotubule agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Coronary spasms/ischaemia</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Myocarditis (rare)</td>
<td></td>
</tr>
<tr>
<td>Genitourinary cancer</td>
<td>Thrombosis</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Bradycardia</td>
<td></td>
</tr>
</tbody>
</table>

Suter and Ewer. Eur Heart Journal, 2013
Cardiotoxicity not new!
Why the interest now?
Cardiotoxicity of Targeted Agents

<table>
<thead>
<tr>
<th>Class/drug</th>
<th>Selected indications</th>
<th>Important CV side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signalling inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HER2</td>
<td>Breast cancer</td>
<td>Cardiac dysfunction</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Gastric cancer</td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiogenesis inhibitors/anti-VEGF</td>
<td>Gastrointestinal cancer</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Renal cell carcinoma</td>
<td>Endovascular damage</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Hepatocellular carcinoma</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCR-ABL inhibitors</td>
<td>Leukaemia</td>
<td>Oedema, cardiac dysfunction (rare)</td>
</tr>
<tr>
<td>Imatinib</td>
<td></td>
<td>QTC prolongation</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Gastric cancer</td>
<td></td>
</tr>
<tr>
<td>Nilotinib</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Suter et al. Eur Heart Journal, 2013
# Cardiotoxicity with VEGF inhibitors

## Table 3. Rates of Hypertension With Selected Angiogenesis Inhibitors

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug</th>
<th>Study</th>
<th>Angiogenic Rates, %</th>
<th>Control Rates, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td>Bevacizumab</td>
<td>Dewdrey 2012,65 Mir 2011,66</td>
<td>11</td>
<td>2.3</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>Bevacizumab</td>
<td>Fraeman 2015,67</td>
<td>36</td>
<td>NA</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Bevacizumab</td>
<td>Mir 2011,66 Chen 2015,68</td>
<td>7</td>
<td>0.7</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Bevacizumab</td>
<td>Fraeman 2013,67</td>
<td>14.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Bevacizumab</td>
<td>Gampenrieder 2014,69</td>
<td>26.4</td>
<td>16.7</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>Sunitinib</td>
<td>Larchelle 2012,71</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>GIST</td>
<td>Sunitinib</td>
<td>George 2012,72</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Sunitinib</td>
<td>Sungjub &amp; Chamberlain 2015,73</td>
<td>6</td>
<td>NA</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Sorafenib</td>
<td>Funakoshi 2013,74</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Cediranib</td>
<td>Langenberg 2009,75</td>
<td>35</td>
<td>NA</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Cediranib</td>
<td>Langenberg 2009,75</td>
<td>42</td>
<td>NA</td>
</tr>
<tr>
<td>Phase I</td>
<td>Sorafenib and bevacizumab</td>
<td>Castellano 2013,76 Azad 2008,70</td>
<td>33</td>
<td>NA</td>
</tr>
</tbody>
</table>

GIST, gastrointestinal stromal tumor; NA, not available.

CA CANCER J CLIN 2016;66:309–325
## Cardiotoxicity and Tyrosine Kinase Inhibitors (CML)

<table>
<thead>
<tr>
<th>Multitargeted tyrosine kinase inhibitors</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
<th>Ponatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL, ABL mutants (except T315I), and other kinases; SRC, KIT, PDGFR, EGFR, BRAF, DDR1, DDR2, ephrin receptors</td>
<td>Pulmonary hypertension, vascular events, prolongation of QT interval corrected for heart rate</td>
<td>Coronary, cerebral, and peripheral vascular events, hypoglycemia, prolongation of QT interval corrected for heart rate</td>
<td>Coronary, cerebral, and peripheral vascular events</td>
</tr>
<tr>
<td>ABL, ABL mutants (except T315I), and other kinases; ABL2 (also called ARG), KIT, DDR3, NQO2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABL, ABL mutants (including T315I), and other kinases; FGFR, VEGFR, PDGFR, ephrin receptors, SRC, KIT, RET, TEK (also called TIE2), FLT3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## CML Patients on TKI

### Annual Rate of Arterial Event (95 percent C.I.)

<table>
<thead>
<tr>
<th></th>
<th>PVD</th>
<th>CAD</th>
<th>CVA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ponatanib</strong></td>
<td>3.9% (2.4-5.3%)</td>
<td>6% (4.2-7.8%)</td>
<td>2.9% (0-4.1%)</td>
</tr>
<tr>
<td><strong>Nilotinib</strong></td>
<td>1.3% (0.8-1.8%)</td>
<td>1.4% (1-1.6%)</td>
<td>0.3% (0.1-0.4%)</td>
</tr>
<tr>
<td><strong>Dasatinib</strong></td>
<td>0.2% (0.1-0.3%)</td>
<td>0.6% (0.3-0.8%)</td>
<td>0.7% (0.4-1.0%)</td>
</tr>
<tr>
<td><strong>Bosotinib</strong></td>
<td>0.1% (0-0.3%)</td>
<td>0.3% (0-0.7%)</td>
<td>0.1% (0-0.4%)</td>
</tr>
<tr>
<td><strong>Imatinib</strong></td>
<td>0.1% (0-0.1%)</td>
<td>0.1% (0-0.1%)</td>
<td>0.1% (0-0.1%)</td>
</tr>
</tbody>
</table>

*Chai-Adisaksopha et al Leukemia & Lymphoma 2015*
Immune checkpoint inhibitors

PD-L1/PD-1 binding inhibits T cell killing of tumor cell

Blocking PD-L1 or PD-1 allows T cell killing of tumor cell

cancer.gov
A 65-year-old woman with metastatic melanoma was admitted to the hospital with atypical chest pain, dyspnea, and fatigue 12 days after receiving her first doses of nivolumab (1 mg per kilogram of body weight) and ipilimumab (3 mg per kilogram).
A clinical scenario

• 65 y.o. female with node positive breast cancer – ER +, PR +, HER2 +
• Oncologist recommends adjuvant anthracycline-based chemotherapy (FEC-D) and Trastuzumab
• History of hypertension and diabetes
• 30 pack year smoking history
• Echocardiogram: EF = 40 %
• What now?
But We Are not Cardiologists!
Figure 1: Interaction Between Shared Risk Factors, Cardiac Disease & Cancer
Optimize Cardiac Health

Best Cancer Care
Ottawa Cardiac Oncology Clinic

Dr. Susan Dent
Medical Oncologist

Dr. Michele Turek
Cardiologist

Dr. Christopher Johnson
Cardiologist

Dr. Angeline Law
Cardiologist

Dr. Ellamae Stadnick
Cardiologist

Dr. Jeffrey Sulpher
Medical Oncologist

Dr. Olexiy Aseyev
Cardiac Oncology Fellow

Jason Wentzell
Pharmacist

Nadine Graham
Research Assistant
Cancer Quality Council of Ontario
2013 Innovation Award
Establishing a Cardio-oncology program

Cardiac Oncology: Improving Cardiac Safety, Advancing Cancer Care

Burgeoning Cardio-Oncology Programs
Challenges and Opportunities for Early Career Cardiologists/Faculty Directors

Tochi M. Okwuosa, DO,* Ana Barac, MD, PhD†

JACC, volume 66, No. 10, 2015

What does a clinic offer?

- Rapid access to cardiologists with an understanding of systemic/targeted therapies.
- Education of patients and health care providers
  - Resident/fellowship training
  - Preceptorship
  - Multidisciplinary rounds
- Development of a collaborative research environment: basic/translational research and clinical/health outcomes research.
Cardio-oncology treatment decision process

Oncology
*Treat Cancer*

Cardio-Oncology assessment

Cardiology
*Treat CV disease*

Cardiovascular risk

Cancer treatment benefits
The Ottawa Cardio-Oncology Program

**Education**
- Multidisciplinary Rounds
- Preceptorship
- Fellowship
- Undergraduate Medical education

**Research**
- Clinical outcomes
- Translational
- Optimal imaging strategies
- Biomarkers
- Database

**Clinical**
- Medical and radiation
- Oncologists/hematologists
- Cardiologists
- Pharmacists
- Nursing

**Cardio-Oncology Clinic**

**Cardio-Oncology Survivorship**
CARDIO-ONCOLOGY PROGRAM
CLINICAL WORK

- SINCE 2008
- > 1,000 patients

PATIENT

CARDIAC RISK FACTORS
PREVENTION STRATEGIES
EARLY DETECTION
IMPROVE CLINICAL OUTCOMES
PREDICTION
COMPLETION OF CANCER TREATMENT

CARDIO-ONCOLOGY SURVIVORSHIP CLINIC

Canadian Cardiac Oncology Network

cardiaconcology.ca
Initial Five Years Experience Of The Ottawa Hospital Cardio-Oncology Clinic: Patient Characteristics & Clinical Outcomes (n=412)

Christopher Johnson, Michele Turek, Angeline Law, Ellamae Stadnick, Sean Hopkins, Nadine Graham, Franco Dattilo, Jeff Sulpher, Susan Dent

Fig 1. Reason For Referral

Presented at Canadian Cardiovascular Society Meeting, Montreal Oct 2013
Initial Five Years Experience Of The Ottawa Hospital Cardio-Oncology Clinic: Patient Characteristics & Clinical Outcomes (n=412)

Christopher Johnson, Michele Turek, Angeline Law, Ellamae Stadnick, Sean Hopkins, Nadine Graham, Franco Dattilo, Jeff Sulpher, Susan Dent

Fig 3. Targeted Therapies: Outcomes In Patients With Mild or Mod/Sev LV Dysfunction
Cardiotoxicity in breast cancer patients: A single center, retrospective review

Moira Rushton, Freya Crawley, Jeffrey Sulpher, Christopher Johnson, Susan Dent

Progress in Pediatric Cardiology, 2015
ESTABLISHING A CARDIAC ONCOLOGY CLINIC - TIPS FOR ACHIEVING SUCCESS

- Logistics
- Resources
- Expertise
- Allied Health Support
- Collaboration

- Location of clinic, close interaction between oncologists and cardiologists
- Access to space, imaging, $$
- Cardiologist with imaging experience and knowledge of cancer therapies
- Support from other health care providers (nursing, pharmacy)
- Consistent communication between health care providers
ESTABLISHING A CARDIAC ONCOLOGY CLINIC - BARRIERS AND OBSTACLES

• lack of Institutional support

• lack of academic and administrative mentorship – novelty of field, a shortage of evidence-based clinical standards

• lack of opportunities for education and training

• limited awareness among oncology and cardiology specialists about the need for cardio-oncology services

Okwuosa and Barac JACC, 2015
A Successful Cardio-Oncology Program
Education

- Multidisciplinary rounds (accredited)
- CME presentations (allied HCP’s)
- Preceptorship program
- Training- Residency/Fellowships
- Cardio-Oncology Meetings (ICOS-NA, GCOS)
- Special education sessions – ASCO, SABCS
- Courses (ACC workshop)
Education

• National Organization (Canadian Cardiac Oncology Network) in 2011
• Website -2013 (www.cardiaconconology.ca)
• ICOS (www.icosna.org)
• ACC – Cardio-Oncology Section (www.acc.org)
• ECOG-ACRIN cardiotoxicity working group
Guidelines/Position Statements

• CCS guideline*
• ASCO survivorship guideline***
• ESC position statement update**
• ESMO guideline update
• ICOS position statement

Education in Cardio-Oncology

ACC pre-assessment report for Advancing Cardiovascular Care of the Oncology Patient
February 2017
Q. Do you think cardiologists/oncologists in general have a good level of understanding of...

Education in Cardio-oncology

Mean: 2.52

Cardiologists: 3% Poor, 18% fair, 27% moderate, 30% good, 17% excellent

Mean: 2.61

Oncologists: 4% Poor, 14% fair, 19% moderate, 43% good, 11% excellent

Barac et al JACC 2015
Research in Cardio-Oncology

Where are we going?
Publications in Cardio-Oncology

Barac A et al. JACC 2015: 65(25): 2739
Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a $2 \times 2$ factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol.

Gulati G$^1$, Heck SL$^1$, Lee AH$^2$, Hoffmann P$^3$, Schulz-Menger J$^4$, Fagerland MW$^5$, Gravdehaug B$^6$, von Knobelsdorff-Brenkenhoff F$^7$, Bratland A$^8$, Storås TH$^9$, Hagve TA$^{10}$, Røsjø H$^1$, Steine K$^1$, Geisler J$^2$, Omland T$^{11}$.

Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101–Breast): A Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity

Edith Pituskin, John R. Mackey, Sheri Koshman, Davinder Jassal, Marshall Pitz, Mark J. Haykowsky, Joseph J. Pagano, Kelvin Chow, ...
React-EF Optimization of cardiac monitoring

Risk prediction of cardiotoxicity

Biomarkers + imaging strategies

Early detection of cardiotoxicity using markers of apoptosis

SAFE study Cardiac protection during cancer treatment

International cardio-oncology registry

198 registered CT on diagnosis and treatment of cardiotoxicity clinical trials.gov
Five centers from Canada, United States, and Spain will be included in the inaugural cardio-oncology registry.

The database will have a web-based interface; a possible platform is the REDcap-project.

**REDCap** is a secure web application for building and managing online databases. It is specifically geared to support data capture for research studies.
What are the Challenges?

• Early identification of cardiac risk
  – e.g cardiac imaging, biomarker

• Strategies to prevent cardiotoxicity
  – Primary and secondary prevention

• Optimal cardiovascular drugs to manage cardiotoxicity

• Surveillance and monitoring
  – Imaging, frequency and duration
Opportunities

“Cardio-oncology partnerships are needed to decrease the burden of cardiotoxicity with our ‘newer’ therapies”

Dr. Christine Brezden-Masley, 2011
Developing a Cardiology-Oncology Partnership
US teen undergoes rare heart-lung transplant
Take Home Messages

• Cancer and heart disease are significant causes of morbidity and mortality in North America

• Improvement in cancer therapies has resulted in long term survivors who may be at risk of cardiotoxicity.

• Individuals with heart disease may develop cancer and require potentially cardiotoxic cancer therapy.
Take Home Messages

• Close collaboration among health care providers is needed in order to provide the best cancer care while optimizing cardiac health

• Research is urgently needed to determine the best prevention, early detection and treatment strategies for patients who experience cardiotoxicity from their cancer treatment
Save the Date

Global Cardio-Oncology Summit 2017
September 20-21, 2017
London, UK

Additional details to follow.

British Cardio-Oncology Society
BC-OS.org

Royal Brompton & Harefield
NHS Foundation Trust

Topics include:

- How to deliver a Cardio-Oncology service
- Training in Cardio-Oncology
- eHealth and Cardio-Oncology
- How do I measure the quality of my service?
- Role of primary care in cancer survivors
- Immunotherapy and emerging cardiotoxicity
- Personalised medicine & genetics
- EP session – who should have ablation, ICDs, CRT?
- Anticoagulation and antithrombotic (AF, ACS)
Thank-you